9. The isolated koji mold of claim 1, wherein the isolated koji mold has at least 3 times greater protease activity and at least 5 times greater peptidase activity than the parent strain.

REMARKS

Applicants respond herein to the Office Action of September 11, 2002. Applicants wish to thank the Office for withdrawing all prior rejections. Applicants have added new claims 8 and 9. Support for both claims can be found throughout the specification, for example, on page 7, first full paragraph, and in Example 1. Thus, the claims are fully supported by the specification.

Applicants will now address the new rejection issued in the Office Action.

Claims 1-7 are rejected under 35 U.S.C. § 103(a) as being unpatentable over either Kauppinen et al. (U.S. Patent No. 5,994,113) or Umitsuki (EP 0 967 286) in view of Murakami et al. (EP 0 427 385). The Office contends that Kauppinen and Umitsuki disclose an expression vector harboring a peptidase gene wherein the gene construct is transformed into a suitable host such as *Aspergillus*. The Office further contends that Murakami discloses a gene expression vector comprising a useful enzyme such as a protease. The construct is alleged to be used to express useful substances in molds such as *A. sojae, A. oryzae, and A. tamarii*. Thus, the Office alleges that it would have been obvious to transform a suitable host such as *A. sojae, A. oryzae, and A. tamarii* with a construct or constructs that comprises both a peptidase or protease. Moreover, the Office alleges that it is well within the purview of the ordinary skilled artisan to make constructs expressing multiple genes or to transform cells with multiple constructs each having the desired gene. The Office furthermore argues that one of ordinary skill in the art would have been motivated to express both these types of enzyme hydrolases because protein hydrosylates are commonly used in food products to perform enzymatic hydrolysis of vegetable,

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yeast or animal proteins. Thus, the Office contends that the invention as a whole would have been *prima facie* obvious to one of skill in the art at the time the invention was made. Applicants respectfully traverse.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. MPEP § 706.02(j).

Applicants believe the Office has failed to meet the first criteria. Motivation to combine the references may be lacking when the references teach away from their combination. MPEP § 2145(X)(C)(2). Claims 1-7 all require a "koji mold having increased protease activity and peptidase activity in relation to a parent strain resulting from transformation with a protease nucleic acid sequence and a peptidase nucleic acid sequence." Kauppinen and Umitsuki disclose a single peptidase gene construct and transformation of only that peptidase gene construct. Kauppinen, moreover, specifically excludes any other peptidase or protease from being transformed into the same host cell. Kauppinen recognizes that a "vast number of enzymes exhibiting peptidase activity are capable of performing enzymatic hydrolysis." (Col. 1, lines 34-35). However, Kauppinen also discusses that "one of the main problems of protein hydrolysates is that they often taste bitter." (Col. 1, lines 26-27). Thus, Kauppinen embarks on transforming

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and producing only one peptidase so that it is not associated with any other peptidases or proteases. Once that peptidase is purified, it may be combined, if necessary, in an enzymatic preparation or composition with other peptidases or proteases to adjust the taste. Specifically, Kaupppinen states the following:

> In general[,] products, [sic] useful for producing protein hydrolysates without a bitter taste, comprise a mixture of peptidase and aminopeptidase activities. It would therefore be desirable to be able to provide a **single-component enzyme (i.e. substantially without any side activity)** exhibiting only an activity useful for reducing the bitterness of protein hydrolysates used in food products.

Col. 2, lines 34-40, emphasis added. Indeed, Kauppinen states under "Summary of the Invention" that:

> The object of the present invention is to provide a single-component enzyme exhibiting an activity...
> The complete DNA sequence encoding said aminopeptidase makes it possible to prepare single-component aminopeptidase.

Col. 2, lines 48-62. By transforming and producing a "single-component enzyme" that has no other enzyme activity but the one that is being transformed, Kauppinen teaches away from transforming another gene that exhibits another enzyme activity. Moreover, the Examples suggest that a protease increases bitterness and therefore it would be undesirable to transform both a peptidase and a protease into the same host cell. In Examples 11 and 12, peptidase produced from a transformed host was added to a bitter-tasting solution containing 8% (w/w) protease hydrolysed whey protein. Upon addition of the peptidase, "the 35 kDa aminopeptidase had debittered the protein hydrolysate samples." Thus, while protease gave the whey protein a bitter taste, the peptidase reduced the bitterness.

Example 13 also suggests that a protease/peptidase combination may not be desirable. In that Example, the flavor, dough stickiness, and crumb structure of bread were compared using a

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commercial product (Flavourzyme®) containing a protease/peptidase complex or just the peptidase produced from a transformed host cell in bread flavor. When Flavourzyme® was used, the crumb structure was found to be "crumby and open" (see Table in Example 13), whereas the "crumb structure is not affected by the aminopeptidase of the invention. The dough stickiness is improved in comparison to the commercial protease/peptidase complex Flavourzyme®." (Col. 24, lines 58-61). Moreover, "the 35 kDa aminopeptidase of the invention gives a significant flavour enhancement in the form of a "fresh baked" bread smell when added in amounts from 30 to 300 LAPU per kg flour." (Col. 24, lines 54-57).

Thus, it is apparent from the entire disclosure of Kauppinen that Kauppinen teaches away from transforming a host cell with both a peptidase and protease. Otherwise, the purpose of being able to adjust the flavor and quality of foods that are bitter would be defeated. Thus, the Office cannot combine the teachings of Murakami which allegedly teaches a gene expression vector comprising a protease.

Moreover, contrary to the Office's contention, Murakami does not teach a gene expression vector comprising a protease. Murakami uses the genomic gene of alkaline protease to isolate its promoter and terminator units to construct a gene expression vector useful for the expression of a protein. However, nowhere does Murakami suggest expressing a protease. Instead, Murakami suggests that "[t]hese promoter and terminator of the present invention may be used in one set as a gene expression unit. By introducing a gene coding for urokinase, hepatitis B antigen, human serum albumin, interferon α or interferon γ or a gene coding for its derivative into the resulting expression vector, further transforming therewith hosts. . . and culturing the transformants, the desire compounds can be obtained." (Page 3, line 58 - page 4,

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line 5). Indeed, Murakami had not contemplated expressing protease, rather, Murakami had intended on expressing heterlogous proteins, i.e., non-protease genes.

The above statement also shows that the utility contemplated by Murakami is different from that of Kauppinen and Umitsuki. Murakami's utility is not for enhancing the flavor of food products, because one clearly would not add a "urokinase, hepatitis B antigen, human serum albumin, interferon α or interferon γ" into food products.

Applicants believe that the Office's conclusion of obviousness is based on improper hindsight. As the Federal Circuit has recognized, the temptation to use hindsight analysis based on Applicant's specification is great and must be guarded against. *Grain Processing Corp. v. American Maize-Prods. Co.*, 840 F.2d 902, 907, 5 U.S.P.Q.2d 1788, 1792 (Fed. Cir. 1988). Even though a protease and aminopeptidase gene were known, no one has transformed both into the same host until the Applicants. As stated in the instant specification, "until now, no attempt had been made to obtain a koji mold having increased activity of both enzymes by transformation using both a protease gene and a peptidase gene, and no such transformant existed." (Page 3, second full paragraph). In conclusion, the Office has shown insufficient motivation to combine the references and therefore has failed to establish a *prima facie* case of obviousness. Applicants respectfully request withdrawal of the rejection.

In view of the foregoing amendments and remarks, Applicants respectfully request the reconsideration and reexamination of this application and the timely allowance of the pending claims.

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The undersigned has been given limited recognition under 37 C.F.R. § 10.9(b) to prosecute this patent application. That document granting limited recognition is enclosed herewith.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

By: _____
Yuko Soneoka
Limited Recognition under
37 C.F.R. § 10.9(b)

Dated: December 6, 2002

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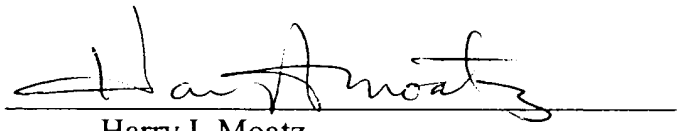

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